

### ***REMARKS***

Claims 1 – 58 are pending in the application. Claims 6, 14-15, 20, 22, 30, and 32-57 have been cancelled. Claims 1, 2, 26 and 58 have been amended. New claim 59 has been added. Applicants reserve the right to prosecute these inventions in one or more continuing applications. Support for the amendments and new claims can be found throughout the claims and specification as filed. No new matter has been added.

### ***Claim Objections***

The Examiner has objected to claims 1 – 13, 16 – 19, 21, 23 – 31, and 58 for minor informalities. The Examiner argues that the claims recite measuring biomarker, Marker I (BC1), Marker II (BC2), Marker III (BC3)...(and) the specification although teaches the molecule weight of the biomarkers...measured by SELDI, neither specification nor claims provide more information such as full name, the abbreviation recognized in the art, or the structures such as sequences or SEQ ID NOs of the biomarkers.” (Office Action, p.2). Applicants disagree.

The claims have been amended to recite that the biomarker comprises an intensity peak in surface enhanced laser desorption/ionization (SELDI), and that the biomarkers having a specified molecular mass. Page 24 of the specification teaches that “biomarkers are represented as intensity peaks in SELDI protein chip/mass spectra with molecular masses centered around the following values:” and then lists the masses (in daltons) that are accurate to within 0.15 percent of the specified value as determined by the disclosed SELDI-mass spectroscopy protocol.” (page 24, lines 1 – 20). Accordingly, the claims recite specific biomarkers as defined by their SELDI intensity peak and corresponding molecular mass. No further information is required or necessary.

Applicants respectfully request that the objection be withdrawn.

### ***Rejection of Claims 1-13, 16-19, 21, 23-31 and 34 Under 35 USC 112, First Paragraph***

The Examiner has indicated that claims 1-13, 16-19, 21, 23-25 and 58 are rejected under 35 USC 112, first paragraph as, allegedly, failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

It is noted that the Examiner considers that “biomarkers, BC2, and BC3...are considered as truncated plasma competent protein, anaphylotoxin C3a, lacking the C-terminal region I.” (Office Action, p.3). The Examiner argues that

The specification provides detailed teachings regarding the claimed methods. For example the specification teaches methods for the detection and diagnosis of cancer comprising

detecting at least one or more protein biomarkers in a subject sample, and;  
correlating the detection of one or more protein biomarkers with a diagnosis of cancer, wherein the correlation takes into account the detection of one or more biomarker in each diagnosis, as compared to normal subjects, wherein the one or more protein markers are selected from Marker I (BC1); Marker II (BC2); Marker III (BC3); Marker IV; Marker V; Marker VII; Marker VIII; Marker IX; Marker X; Marker XI; Marker XII; Marker XIII; and Marker XIV, and combinations thereof.

In a preferred method for detection, diagnosis and determination of the clinical stage of breast cancer, comprises detecting at least one or more protein biomarkers in a subject sample, wherein the protein markers are selected from Marker I (BC1); Marker II (BC2); Marker III (BC3), combinations thereof; and; correlating the detection of one or more protein biomarkers with a diagnosis of breast cancer, wherein the correlation takes into account the detection of one or more protein biomarkers in each diagnosis, as compared to normal subjects.

See page 6, lines 5-20.

The specification further provides detailed teachings regarding how to obtain biological samples from subjects and how to measure the amount of the claimed biomarkers in the sample.

Moreover, there are a number of working examples that are demonstrate that the claimed methods are enabled. For example, the specification teaches that the claimed methods demonstrate

[t]he high specificity and sensitivity of the method used for identifying the biomarkers that differentiate between the different stages of breast cancer is underscored by using only three of these biomarkers, 4283 (BC1), 8126 (BC2) and 8932 (BC3), to correctly identify 93% of breast cancer patients at different stages: Stage 0/I (93%), stage II (85%) and stage III (94%). Using only one biomarker (BC3), correct identification 85% of breast cancer patients with stage 0/I (88%), stage II (78%) and stage III (92%) was achieved.

In particular, simultaneous analysis of protein profiles of 169 serum samples of subjects with or without breast cancer using was carried out and the results demonstrate the high specificity and selectivity of the methods described herein. Out of the 169 serum samples of subjects, three discriminating biomarkers were identified, the combination of which achieved both high sensitivity (93%) and high specificity (91%) in detecting breast cancer from the non-cancer controls.

See page 25, line 14-26 of the specification.

Additionally, the Examples set forth the following tables summarize the results obtained using the identified markers. The ability of the claimed methods to accurately identify subjects having breast cancer is set forth demonstrated by the data set forth in the following tables from Examples 4 and 5.

Table 1

	Non-cancer Controls (n=66)		Breast Cancer Patients Stages 0-I (n=42)		Breast Cancer Patients Stages II-III (n=61)	
	Mean	Stdev	Mean	Stdev	Mean	Stdev
BC1	0.302	0.312	-0.118	0.244	-0.081	0.258
BC2	0.981	0.358	1.411	0.154	1.295	0.205
BC3	0.526	0.252	0.993	0.193	1.003	0.234
Comp. Index	-0.375	0.313	0.425	0.257	0.349	0.242

Table 2A. Diagnostic performance of BC3.

Cutoff=0.8	Non-Cancer Controls			Breast Cancer Patients			
				Stage			
		Benign	Subtotal	0-I	II	III	Subtotal
	0	6	6	37 (88%)	29 (78%)	22 (92%)	88 (85%)
Negative	41 (100%)	19 (76%)	60 (91%)	5	8	2	15
Total	41	25	66	42	37	24	103

Table 2B. BootStrap estimated diagnostic performance of logistic regression derived composite index using BC1, BC2 and BC3 (20 runs, leave out rate = 30%).

LR at cutoff=0	Non-Cancer Controls			Breast Cancer Patients			
				Stage			
		Benign	Subtotal	0-I	II	III	Subtotal
				93%	85%	94%	93% (85-100%)
Negative	100%	85%	91% (82 - 100%)				

Clearly, the teachings of the specification and the extensive working examples enable the claimed methods.

The Examiner cites a number of references to support the enablement rejection, but each of these references was published after the priority date of the instant application. Enablement is determined as of the effective filing date of the patent, In re Hogan, 559 F.2d 595, 604 (CCPA 1977). The use of the post-filing references by the Examiner is improper.

The Examiner points out that post filing references can be used to prove that, at the time of filing, the claimed invention was not possible. However, we disagree with the Examiner's characterization of these references and the teachings they provide.

The Examiner has cited Li et al. (2005, *Clinical Chemistry*) and believes that that this publication "has invalidated the biomarker BC1 for breast cancer determination". Applicants disagree. A critical reading of Li et al. demonstrates that BC1 is a valid biomarker for the detection of breast cancer. Specifically, the authors state on page 2234, second column, that "BC1 may still be a valid marker if serum were collected prospectively and stored under the same conditions".

Moreover, the Examiner cites references and states that these references demonstrate that BC2 and BC3 are not valid biomarkers for the determination of breast cancer status. Applicants again disagree. Applicants show data demonstrating that these two markers can discriminate

between benign and cancerous tissue (see the data presented in the Examples of the instant application).

Accordingly, based on the extensive teachings in the specification, and the working examples, the invention is clearly enabled by the specification as filed. Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

***Rejection of Claims Under 35 USC 102(b)***

The Examiner has rejected claims 1, 2, 4, 5, 7, 13, 16, 17, 23, 25 and 58 as being anticipated by Watson et al. Applicants respectfully traverse this rejection. The claims have been amended to indicate that the biomarkers of the instant invention are identified by mass spectrometry, and therefore are not anticipated by Watson et al. Watson et al. only teach the detection of mammaglobin by immunoassay. Moreover, the claims have been amended to indicate the molecular weight of each marker. Watson et al. does not teach or suggest biomarkers with the claimed molecular weights.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

***Rejection of Claims Under 35 USC 102(e)***

The Examiner has rejected claims 1, 2, 4-8, 10, 11, 17-19, 21, 23, 24, 26-28, 30 and 58 as being anticipated by Mutter et al. As indicated above, the claims have been amended to indicate the molecular weights of the claimed biomarkers. Mutter et al. does not teach or suggest the biomarkers as currently claimed.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

***Rejections Under 35 USC 103(a)***

The Examiner has rejected claims 1-3, 8-12, 26 and 29 under 35 USC 103(a) as being unpatentable over Watson et al. in view of Lauro et al. and/or Gion et al. As indicated above, the amended claims are not anticipated by Watson et al. Moreover, Lauro et al. nor Gion et al. make up for the deficiencies of Watson et al.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

The Examiner has rejected claims 26 and 31 under 35 USC 103(a) as being unpatentable over Mutter et al. in view of Watson et al. As indicated above, the amended claims are not anticipated by Watson et al. nor Mutter et al. Moreover, Watson et al. does not make up for the deficiencies of Watson et al.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

**REMARKS**

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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